EPA Reviewer: Linnea J. Hansen, Ph.D. Linnea J. Hansen, Date 3/22/99
Toxicology Branch I (7509C)
EPA Secondary Reviewer: Susan Makris, M.S. Susan A Makris, Date 3/23/99
Toxicology Branch I(7509C)

Note: This executive summary is an addendum to a DER dated 1/19/96 (HED Doc. No. 011748)

DATA EVALUATION RECORD

STUDY TYPE: 2-Generation Reproductive Toxicity (Dietary) - Rat [§83-4]

MRID NOS.: 42899101 through -05 and 43624401

DP BARCODE: D241367 SUBMISSION CODE: S511876
P.C. CODE: 102001 TOX. CHEM. NO.: 375A

TEST MATERIAL (PURITY): Thiophanate-methyl (95.9% a.i.)

SYNONYMS: Topsin® M; Dimethyl 4,4'-o-phenylenebis (3-thioallophanate); 1,2-bis(3-methoxycarbonyl-2-thioureido)benzene

CITATION: (1) Müller, W. (1993) Two Generation Oral (Dietary Administration Reproduction Toxicity Study in the Rat (With One Litter in the P and Two Litters in the F1 Generation). Hazleton Deutschland GmbH, Münster, Germany. Laboratory Project No. 996-683-004. August 20, 1993 (MRIDs 42799101 through -05).

(2) Müller, W. And Singer, A. (1995) Final Addendum Histopathology Report and Peer Review Pathology Report to MRID 42899101: Topsin M: Two Generation Oral (Dietary Administration Reproduction Toxicity Study in the Rat (With One Litter in the P and Two Litters in the F1 Generation). Hazleton Europe and Battelle. Laboratory Project No. 683-004. Unpublished. (MRID 43624401)

SPONSOR: Elf Atochem (Formerly sponsored by Pennwalt Corporation)

EXECUTIVE SUMMARY: Topsin-M (95.9% a.i.) was tested in a two-generation reproduction study with male and female Sprague-Dawley Crl:CD(SD)BR rats (MRIDs 42899101 to -05, 43624401). The rats were administered the test material in the diet at concentrations of 0, 200, 630, or 2000 ppm (calculated to be 0, 13.7, 43.3 or 138.9 mg/kg/day for males and 0, 15.5, 54.0 or 172.0 mg/kg/day for

females). Twenty-five animals/sex/dose/generation were selected for testing. The P generation animals were given test or control diet for 14 weeks (98 days) then mated to produce the F_1 animals. Approximately 14 weeks after weaning of all F_1 offspring, selected F_1 animals were mated within the same dose group for a maximum of 21 days (sibling matings were avoided) to produce the F_{2a} generation. After weaning of the F_{2a} pups, F_1 animals were maintained for 6 weeks and mated again to the same partner to produce the F_{2b} offspring. The second mating of the F_1 animals was performed due to a high, unexplained death rate in the F_{2a} treated and control pups during lactation. All animals were exposed to test material, either in the diet or during lactation, until sacrifice.

No clinical signs of toxicity or mortalities in the parental animals of either generation were attributable to treatment. There were no significant differences in body weights of the P generation high-dose males and the F_1 mid- and high dose males during the pre-mating periods when compared to controls, however, there was a slight dose-related reduction in body weights throughout the study. The premating period (days 1-43) body weight gains in the 630 and 2000 ppm F_{1b} males were less than controls: 56 and 55% of the control value, respectively. These were considered to be borderline significant because the changes were in the range of 5% of the total bodyweight. In females, although there were some decreases in bodyweight and bodyweight gain during gestation, these were not consistent across generations and/or litters and were thus not biologically significant. High-dose P generation males and females and high-dose F_1 males had significantly ($p \leq 0.05$) increased liver and thyroid weights and high-dose F_1 females had increased thyroid weights when compared to controls. Increased organ weights correlated with statistically significant increases in hepatocellular hypertrophy and thyroid follicular cell hyperplasia/hypertrophy in the high dose group. Generally, minimal to slight hepatocellular hypertrophy and thyroid follicular cell hypertrophy and hyperplasia were observed in both the low and mid-dose P generation males. These effects were observed in the F_1 generation but appeared in fewer animals and were less severe. In females, these effects were considerably less. **Therefore, the NOEL for systemic toxicity is <200 ppm (<13.7 mg/kg/day) based on hepatocellular hypertrophy and thyroid follicular cell hypertrophy/hyperplasia at all dose levels and decreased body weight gains in males and increased liver and thyroid weights in both sexes at the highest dose level. This LOEL is considered to be a borderline NOEL/LOEL because the**

effects on the thyroid and liver at 200 ppm were minimal and they were less in the succeeding generation.

No treatment-related effects were noted on the reproductive performance indices of either generation. Mean litter sizes, survival indices, and sex ratios were not different between treated and control groups for the F_1 and F_{2b} offspring. Due to a high rate of death in both the treated and control F_{2a} pups, a second mating of the F_1 animals was made to produce the F_{2b} offspring. Deaths of the F_{2a} pups did not appear to be treatment-related as controls were equally affected and the result was not repeated after the second mating. No statistically significant differences occurred in mean pup weights from any treated group at any time during lactation of the F_1 or F_{2a} pups. However, F_{2b} pups gained less weight than controls with day 21 body weights of 630 and 2000 ppm group males and females being 88% of the control value. When mean pup weights for the F_{2b} litters were analyzed by covariance analysis (ANCOVA) to account for the number of pups per litter, significantly lower weights as compared to control were seen for the 630 ppm males and females on day 1 ($p \leq 0.01$), 2000 ppm males on day 21 ($p \leq 0.05$), and 630 and 2000 ppm females on day 21 ($p \leq 0.05$). Decreased F_{2b} pup weights were not coincident with reduced dam weights since high-dose dams actually gained slightly more than controls during lactation. **Therefore, the LOEL for offspring toxicity is 630 ppm (43.3 mg/kg/day) based on reduced body weights of the F_{2b} pups during lactation. The corresponding NOEL is 200 ppm (13.7 mg/kg/day). This LOEL is also considered to be borderline because the decrease in pup weights was minimal. The reproductive toxicity LOEL is >2000 ppm (138.9 mg/kg/day) and the NOEL is ≥2000 ppm.**

This study is classified as Acceptable and satisfies the guideline requirements for a multigeneration reproduction feeding study (83-4).

DATA EVALUATION REPORT

TOPSIN-M

STUDY TYPE: MULTIGENERATION FEEDING - RAT (83-4)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
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Task Order No. 94-34B

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Disclaimer

This final DER may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

*Managed by Lockheed Martin Energy Systems for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

[TOPSIN-M] Reproduction Study (83-4)

EPA Reviewer: P. Hurley, Ph.D. Pamela M Hurley Date: 11/28/95
Review Section I, Toxicology Branch I (7509C)
EPA Section Head: M. Copley, D.V.M., D.A.B.T. Marion Copley Date 11/28/95
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Multigeneration Reproduction - Rat (83-4)

TOX. CHEM. NO: 375A

P.C. CODE.: 102001

MRID NOS.: 42899101, 42899102, 42899103, 42899104, 42899105, 43624401

TEST MATERIAL: Topsin-M

SYNONYMS: Thiophanate methyl, Cercobin-M

STUDY NUMBER: 683-004

SPONSOR: Nippon Soda Co., LTD, Tokyo, Japan; Elf Atochem North America, Philadelphia, PA

TESTING FACILITY: Hazleton Deutschland GmbH, Kesselfeld 29, 48163 Münster, Germany

TITLE OF REPORT: Two Generation Oral (Dietary Administration) Reproduction Toxicity Study in the Rat (with One Litter in the P and Two Litters in the F1 Generation)

AUTHOR: Wolfgang Müller and Allen Singer

REPORT ISSUED: August 20, 1993; March 29, 1995 (Addendum)

EXECUTIVE SUMMARY: Topsin-M (95.9% a.i.) was tested in a two-generation reproduction study with male and female Sprague-Dawley Crl:CD(SD)BR rats (MRID 42899101-05, 43624401). The rats were administered the test material in the diet at concentrations of 0, 200, 630, or 2000 ppm (calculated to be 0, 13.7, 43.3 or 138.9 mg/kg/day for males and 0, 15.5, 54.0 or 172.0 mg/kg/day for females). Twenty-five animals/sex/dose/generation were selected for testing. The P generation animals were given test or control diet for 14 weeks (98 days) then mated to produce the F_1 animals. Approximately 14 weeks after weaning of all F_1 offspring, selected F_1 animals were mated within the same dose group for a maximum of 21 days (sibling matings were avoided) to produce the F_{2a} generation.

After weaning of the F_{2a} pups, F_1 animals were maintained for 6 weeks and mated again to the same partner to produce the F_{2b} offspring. The second mating of the F_1 animals was performed due to a high, unexplained death rate in the F_{2a} treated and control pups during lactation. All animals were exposed to test material, either in the diet or during lactation, until sacrifice.

No clinical signs of toxicity or mortalities in the parental animals of either generation were attributable to treatment. There were no significant differences in body weights of the P generation high-dose males and the F_1 mid- and high dose males during the pre-mating periods when compared to controls, however, there was a slight dose-related reduction in body weights throughout the study. The premating period (days 1-43) body weight gains in the 630 and 2000 ppm F_{1b} males were less than controls: 56 and 55% of the control value, respectively. These were considered to be borderline significant because the changes were in the range of 5% of the total bodyweight. In females, although there were some decreases in bodyweight and bodyweight gain during gestation, these were not consistent across generations and/or litters and were thus not biologically significant. High-dose P generation males and females and high-dose F_1 males had significantly ($p \leq 0.05$) increased liver and thyroid weights and high-dose F_1 females had increased thyroid weights when compared to controls. Increased organ weights correlated with statistically significant increases in hepatocellular hypertrophy and thyroid follicular cell hyperplasia/hypertrophy in the high dose group. Generally, minimal to slight hepatocellular hypertrophy and thyroid follicular cell hypertrophy and hyperplasia were observed in both the low and mid-dose P generation males. These effects were observed in the F_1 generation but appeared in fewer animals and were less severe. In females, these effects were considerably less. **Therefore, the NOEL for systemic toxicity is < 200 ppm based on hepatocellular hypertrophy and thyroid follicular cell hypertrophy/hyperplasia at all dose levels and decreased body weight gains in males and increased liver and thyroid weights in both sexes at the highest dose level. This LOEL is considered to be a borderline NOEL/LOEL because the effects on the thyroid and liver at 200 ppm were minimal and they were less in the succeeding generation.**

No treatment-related effects were noted on the reproductive performance indices of either generation. Mean litter sizes, survival indices, and sex ratios were not different between treated and control groups for the F_1 and F_{2b} offspring. Due to a high rate of death in both the treated and control F_{2a} pups, a second mating of the F_1 animals was made to produce the F_{2b} offspring. Deaths of the F_{2a} pups did not appear to be treatment-related as controls were equally affected and the result was not repeated after the second mating. No statistically significant differences occurred in mean pup weights from any treated group at any time during lactation of the F_1 or F_{2a} pups. However, F_{2b} pups gained less weight than controls with day 21 body weights of 630 and 2000 ppm group males and females being 88% of the control value. When mean pup weights for the F_{2b} litters were analyzed by covariance analysis (ANCOVA) to account for the number of pups per litter, significantly lower weights as compared to control were seen for the 630 ppm males

and females on day 1 ($p \leq 0.01$), 2000 ppm males on day 21 ($p \leq 0.05$), and 630 and 2000 ppm females on day 21 ($p \leq 0.05$). Decreased F_{2b} pup weights were not coincident with reduced dam weights since high-dose dams actually gained slightly more than controls during lactation. **Therefore, the LOEL for reproductive toxicity is 630 ppm based on reduced body weights of the F_{2b} pups during lactation. The corresponding NOEL is 200 ppm. This LOEL is also considered to be borderline because the decrease in pup weights was minimal.**

This study is classified as Acceptable and satisfies the guideline requirements for a multigeneration reproduction feeding study (83-4).

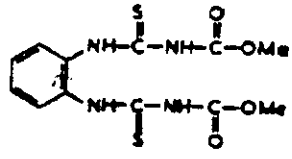
Special Review Criteria (40 CFR 154.7) None

I. MATERIALS AND METHODS

A. MATERIAL

1. Test material: Topsin-M

Description: rose-colored powder
Lot/Batch No.: TIF 01016
Purity: 95.93% a.i.
Stability of compound: not given; stored at room temperature
CAS No.: 23564-05-8
Structure:



2. Vehicle and/or positive control

Basic powdered diet (Ssniff R 10) was used as the vehicle and control.

3. Test animals

Species: rat
Strain: Sprague Dawley Crl: CD (SD)BR
Age and weight at start of study: at least 6 weeks old; males: 186-288 g; females: 158-229 g
Source: Charles River Wiga GmbH, 97633 Sulzfeld, Germany
Housing: Rats were housed individually, except during mating and lactation, in solid floor macrolone cages with stainless steel lids.

Environmental conditions:
Temperature: 19-25°C
Humidity: 30-70%
Air Changes: not given
Photoperiod: 12 hour light/dark cycle
Acclimation period: at least 7 days

4. Diet preparation and analysis

Diet was an admixture of basic powdered diet and test material. Fixed concentrations of a premixture for each treatment group were prepared at 28-day intervals. The premixture was used for subsequent dilution to final volume and concentration. Formulations were stored at room temperature. Concentration and homogeneity were tested in all formulations throughout the study and stability was tested in the initial formulations.

Results -

a. Homogeneity analysis - Separate duplicate samples were taken from the top, middle, and bottom of each test formulation. Results showed the test material to be homogeneously admixed with the powdered diet with concentrations varying <20% from top to bottom.

b. Stability analysis - The initial test formulations were analyzed for stability at room temperature or "deep-frozen" for up to 35 days. All formulations were within ±4% of their initial measured concentration or ±5% of nominal after 35 days.

c. Concentration analysis - Absence of test material was confirmed in control diets. The concentration of test material as compared to expected target ranged from 81-114% in the 200 ppm diet, 89-120% in the 630 ppm diet, and 89-112% in the 2000 ppm diet.

5. Diet

Animals received powdered diet (Ssniff R 10; Ssniff Spezialdiäten GmbH, 59494 Soest, Germany) and water *ad libitum*.

B. PROCEDURES AND STUDY DESIGN

1. Animal assignment

Upon arrival at the testing facility, the P generation male and female rats were examined for signs of ill health. If judged suitable as experimental animals, they were randomly allocated to treatment groups by a stratified randomization procedure based on body weight and by use of a random table of the letters A to D representing the groups 1 to 4. The F_1 males and

females were selected from the F_1 generation by lot. Animal assignment is given in Table 1.

TABLE 1. ANIMAL ASSIGNMENT

Dose Group	Conc. in Diet* (ppm)	No. of Animals per Group			
		P Generation		F_1 Generation	
		Male	Female	Male	Female
1 (Control)	0	25	25	25	25
2 (Low)	200	25	25	25	25
3 (Mid)	630	25	25	25	25
4 (High)	2000	25	25	25	25

*Test or control diets were freely available to the animals from the start of treatment until necropsy.

2. Dose selection rationale

Doses were selected on the basis of a dose range-finding study in male and female Sprague-Dawley rats in which doses of 75, 200, 1200, and 6000 ppm were used (HD Project No. 683-003). The results of this study were summarized in MRID No. 428991-01. At the high-dose level, markedly reduced body weight gain, reduced feed consumption, and markedly increased thyroid weights occurred in males and females. Slightly reduced body weight gain in males and moderately increased thyroid weights in males and females were seen at 1200 ppm. No systemic effects were noted at ≤200 ppm. Although a duration of exposure was not given, the authors state that reproductive performance of the P generation and development of the F_{1a} offspring were not affected.

3. Mating procedure

Each male was mated with one female from the same dose group for up to 3 weeks. Females which had not shown evidence of mating within 2 weeks were paired with proven males of the same dose group for the remainder of the mating period. Vaginal smears were examined in the morning for the presence of sperm or a vaginal plug. The day on which sperm or a vaginal plug was observed was designated gestation day (GD) 0. Mated females were separated from the males and returned to individual housing.

4. Mating schedule

The P generation animals were given test or control diet for 14 weeks then mated for a maximum of 21 days to produce the F_1 animals. Approximately 14 weeks after weaning of all F_1 offspring, selected F_1 animals were mated within the same dose group for a maximum of 21 days (sibling matings were avoided) to produce the F_{2a} generation. After weaning of the F_{2a} pups, F_1 animals were maintained for 6 weeks and mated again to the same partner to produce the F_{2b} offspring.

C. METHODS

1. Observation Schedule

a. Parental animals - All animals were examined twice daily for mortality and morbidity and once daily for signs of overt toxicity. Body weights of all males and females were recorded once weekly during the premating and the mating periods and at sacrifice. Additionally, body weights of females were recorded on GD 0, 7, 14, and 20 and during lactation on days 1, 4, 7, 14, and 21 post partum. Premating food consumption for all males and females was recorded twice weekly at 3- or 4-day intervals. Food consumption was also recorded for females on GD 0, 3, 7, 10, 14, 17, and 20 and on lactation days 0, 4, 7, 9, 11, and 13.

Blood samples were taken from 10 male and 10 female animals per group during the first week of treatment, during week 8, and at necropsy. Blood samples were taken from identical animals each time, if possible. Serum was submitted for thyroid hormone determination. T_3 and T_4 were analyzed by luminescence immunoassay and TSH was analyzed by radio immunoassay.

b. Reproductive performance - For each pregnant female, the date of mating, the date of parturition, the duration of gestation, any abnormalities of nesting or nursing behavior, and the number of implantations (uteri stained at necropsy) were recorded.

The following reproductive indices were calculated (note: the reviewer is interpreting "inseminated" as plug- or sperm-positive; therefore, with this definition, the insemination index is the mating index):

Mean cohabitation days until GD 0 = sum of days until successful insemination/no. of inseminated animals

Insemination index = (No. inseminated animals/Total no. paired animals) × 100

Fecundity index = (No. pregnant animals/Total no. inseminated animals) × 100

Fertility index = (No. pregnant animals/Total no. paired animals) × 100

Gestation index = (No. females with pups born alive/No. pregnant animals) × 100

c. Litter observations - All females were allowed to litter and the number of live and dead pups was determined. The pups were sexed, examined for external abnormalities, and weighed on days 1, 4, 7, 14, and 21 post partum. On day 4 post partum, each litter was adjusted to 4 male and 4 female pups where possible by eliminating extra pups by random selection. Pups dying or killed during lactation were examined for external and visceral abnormalities. The following litter indices were calculated:

Live birth index = (No. pups born alive/No. pups born) × 100

Viability index = (No. pups alive on day 4 precull/No. pups born alive) × 100

Weaning index = (No. pups alive day 21/No. pups alive day 4 postcull) × 100

Proportion of males pups on day 1 and 21 = (No. of males/No. of pups) × 100

During lactation, the pups in each litter were examined daily and physical development was assessed by monitoring pinna unfolding (the day on which the pinnae became detached), tooth eruption (the day on which the upper incisors were observed to penetrate the gum), and eye opening (the day on which the upper and lower eyelids separated). For each event, the number of pups in each litter showing the observation was recorded daily until all the pups in the litter showed the observation. For each pup, the following functional tests were also performed: surface righting reflex, day 8; gripping reflex, day 17; pupillary reflex, day 21; and auditory response, day 21.

2. Postmortem Studies

a. Sacrifice - All surviving animals were killed at scheduled sacrifice by carbon dioxide inhalation.

b. Necropsy -

1) Parental animals - All surviving parental male and female animals of the P generation were sacrificed and necropsied after weaning of the F_1 progeny. All male and female parental animals of the F_1 generation were killed and necropsied after weaning of the F_{2b} offspring. Any animal not surviving until scheduled sacrifice was necropsied as soon as possible.

2) Offspring - Non-selected F_1 weanlings were killed after selection of the F_1 parental animals and all F_{2a} and F_{2b} weanlings were killed and necropsied soon after weaning.

3) Necropsy observations - Gross necropsy consisted of external and internal examinations. The following tissues (X) of all parental animals of the P and F_1 generations were preserved in 10% neutral buffered formalin (except testes and epididymides which were fixed in Bouin's solution) and weighed (XX) (paired organs were weighed separately). With the exception of the liver and thyroid, the tissues of the control and high-dose group animals were imbedded in paraffin wax, sectioned, stained with hematoxylin and eosin, and examined histologically. Microscopic examinations of the liver and thyroid were conducted with all dose levels.

X	Ovaries	XX	Epididymides	XX	Liver
X	Uterus	X	Prostate	X	Pituitary
X	Vagina	X	Seminal vesicles	XX	Thyroids
X	Cervix	X	Coagulating gland		
X	Lesions	XX	Testes		

D. STATISTICAL ANALYSIS

For body weight, body weight change, food consumption, duration of gestation, implantation sites, pups delivered, and live pups per litter the Levene's test for homogeneity of variances was performed followed by rank transformation (if heterogeneous) and the Analysis of Variance (ANOVA). If the ANOVA was significant, Dunnett's two-tailed t-test was used to compare each treated group with the control. For heterogeneous variances of the rank transformed data, the Levene's test was performed again followed by the ANOVA and Dunnett's t-test.

For body weight at necropsy, organ weights, cohabitation days, hormone analysis, physical development, and functional tests Bartlett's test for homogeneity of variances was performed followed by the one-way ANOVA on homogeneous data. In the event of significant results of the ANOVA, the Dunnett's two-tailed t-test was used to compare each treated group with the control. For heterogeneous data, the Kruskal-Wallis test was performed together with the Wilcoxon rank-sum test to compare treated to control groups.

For pup weight per litter, the Analysis of Covariance (ANCOVA) was performed. If the ANCOVA was significant, the Dunnett's two-tailed t-test was used to compare each treated group to the control.

All significant differences were set at $p \leq 0.05$. Reproductive indices were calculated on the basis of individual values and not group totals or group means.

E. Signed and dated GLP and Quality Assurance statements were provided.

II. RESULTS

A. SYSTEMIC TOXICITY

1. Mortality and clinical signs

Clinical signs of toxicity in the P generation consisted of sporadic incidences of alopecia and minor injuries in males and females and vaginal discharge in females. None of these appeared to be dose- or treatment-related. No mortalities occurred in the males of the P generation but 4 females died during the study. One control animal died on day 136 (36 days after insemination; pregnancy status not determinable) and one 200 ppm animal died on day 155 (55 days after insemination; pregnancy status not determinable) of treatment without having shown any clinical signs prior to death. Another 200 ppm female was found dead on day 138 (38 days after insemination; not pregnant) after having shown poor physical condition, lacrimation, and rough haircoat on the same day. One female in the 630 ppm group died on day 122 of the study during delivery. These deaths are not considered to be compound-related.

Clinical signs of toxicity in the F_1 animals occurring prior to, during, and after the first and second matings included alopecia, rough haircoat, and bloody crust around the eyes of both males and females and vaginal discharge in females. Incidences were sporadic and occurred in only a few animals and are not considered to be treatment-related. One 630 ppm male died on day 49 and one 2000 ppm male died on day 23 of the study. After the first mating, one low-dose female died 2 days after delivery with clinical signs the day before noted as pale and cool to the touch. After the second mating, three other females died. One control animal died on day 69 showing red vaginal discharge and incomplete delivery; one 200 ppm animal also died on day 69 (3 days after normal delivery) after having vaginal discharge and being pale and cool to the touch the previous day; and one 630 ppm animal died on day 84 three days after an incomplete delivery and after having been hunched and pale the day before. These deaths are not considered to be compound-related.

2. Body weight and food consumption

a. Premating – There were no significant differences in body weights of treated males as compared to controls; however, there was a slight dose-related reduction in body weights throughout the study. Final mean body weight for the 2000 ppm males was 94% of controls. No differences in food consumption were seen between treated and control males at any time. Body weights and selected food consumption values for P generation males are summarized in Table 2.

TABLE 2. MALES: P GENERATION MEAN BODY WEIGHTS AND FOOD CONSUMPTION

Day of Study	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Body Weight (g)				
Day 1	261.7 ± 23.4	260.2 ± 18.7	260.0 ± 22.5	259.6 ± 17.7
Day 15	358.8 ± 35.9	365.4 ± 28.9	352.7 ± 34.2	352.2 ± 24.7
Day 29	414.8 ± 47.6	425.1 ± 37.9	409.2 ± 44.7	407.7 ± 32.7
Day 50	459.6 ± 58.5	462.0 ± 54.2	449.0 ± 56.7	448.7 ± 36.5
Day 71	487.9 ± 44.4	496.8 ± 57.4	476.1 ± 59.3	476.4 ± 37.2
Day 99 (end of premating period)	552.8 ± 53.1	547.3 ± 65.1	535.6 ± 60.6	525.0 ± 38.1
Day 120 (end of mating period)	556.8 ± 51.5	550.5 ± 66.2	548.1 ± 62.2	537.0 ± 41.2
Day 134 (end of study)	577.1 ± 48.2	564.8 ± 62.5	557.9 ± 67.6	544.5 ± 49.7
Body Weight Gain, Day 1-134	315.4 ± 41.1	304.6 ± 55.6	297.9 ± 52.6	285.0 ± 47.4
Food Consumption Prior to Mating (g)				
Day 1-8	32.2 ± 4.8	33.5 ± 3.1	32.8 ± 3.8	32.9 ± 2.8
Day 8-15	32.1 ± 3.2	32.9 ± 3.0	32.1 ± 3.2	31.5 ± 2.9
Day 22-29	31.4 ± 5.0	32.6 ± 3.2	31.7 ± 4.0	30.7 ± 3.2
Day 43-50	31.1 ± 3.8	31.5 ± 5.5	30.9 ± 5.2	30.7 ± 3.1
Day 64-71	28.3 ± 5.0	28.9 ± 4.3	28.5 ± 4.2	29.6 ± 2.6
Day 92-99	32.3 ± 3.6	30.5 ± 3.8	31.7 ± 3.3	31.4 ± 3.2
Day 1-99	30.9 ± 3.2	31.2 ± 3.0	30.7 ± 3.4	30.8 ± 2.0

Data taken from Table 3, p. 115-116, Table 4, p. 121-122, and Table 9, p. 131-132, MRID No. 428991-01.

Mean body weight change for the high-dose P generation females was slightly lower than controls for the entire premating period but there were no differences in final body weights. During the first week, 630 ppm females ate significantly more than controls but there were no other differences in food consumption between treated and control groups. Body weights and selected food consumption values for P generation females are summarized in Table 3.

TABLE 3. FEMALES: P GENERATION MEAN BODY WEIGHTS AND FOOD CONSUMPTION PRIOR TO MATING

Day of Study	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Body Weight (g)				
Day 1	200.5 ± 10.1	202.9 ± 12.1	204.1 ± 11.1	203.2 ± 14.0
Day 15	234.3 ± 16.3	235.4 ± 12.6	236.2 ± 14.9	234.9 ± 14.5
Day 29	248.1 ± 13.5	256.2 ± 17.0	257.2 ± 18.7	253.6 ± 15.4
Day 50	269.5 ± 17.3	270.7 ± 18.3	274.4 ± 20.2	268.7 ± 19.5
Day 71	274.7 ± 15.7	279.1 ± 20.8	283.4 ± 22.9	278.6 ± 18.3
Day 99	295.6 ± 18.8	296.3 ± 27.4	302.9 ± 25.2	295.1 ± 20.5
Body Weight Gain, Day 1-99	95.1 ± 16.2	93.4 ± 23.2	98.9 ± 22.4	91.9 ± 16.8
Food Consumption (g)				
Day 1-8	21.4 ± 1.9	22.0 ± 1.5	22.6 ± 1.9*	21.2 ± 1.3
Day 8-15	21.8 ± 2.1	21.9 ± 1.4	22.8 ± 2.8	21.7 ± 1.4
Day 22-29	21.6 ± 2.3	22.5 ± 1.9	22.7 ± 3.2	21.9 ± 2.3
Day 43-50	22.2 ± 2.6	22.0 ± 2.2	22.3 ± 2.9	21.4 ± 2.0
Day 64-71	20.5 ± 2.5	20.1 ± 2.1	21.1 ± 2.8	20.8 ± 2.0
Day 92-99	21.4 ± 3.3	21.4 ± 2.7	22.4 ± 3.3	21.4 ± 2.4
Day 1-99	21.4 ± 2.0	21.6 ± 1.6	22.1 ± 2.4	21.3 ± 1.2

Data taken from Table 3, p. 117-118, Table 4, p. 123-124, and Table 9, p. 133-134, MRID No. 428991-01.
*Significantly different from control, $p \leq 0.05$.

Selected body weights and food consumption data for F_1 males prior to and during the first and second matings are listed in Tables 4 and 5, respectively. F_1 males in the 630 and 2000 ppm groups generally gained less weight throughout the study than controls. This resulted in lower mean body weights for these groups after day 50 prior to the first mating with the difference becoming more pronounced through day 113. At the start of treatment prior to the second mating (Table 5), body weights for the males were comparable between the mid- and high-dose groups and the control. However, treated animals in these groups again gained less weight than controls resulting in lower mean body weights. Overall body weight gains in the 630 and 2000 ppm animals prior to the second mating were less than controls: 56 and 55% of the control value, respectively. However, these are considered to be borderline significant because the decreases were in the range of 5% of the total bodyweight. The only significant difference in food consumption for these two groups occurred prior to the second mating with the high-dose animals eating less than controls ($p \leq 0.05$) during the day 15-22 interval. The 200 ppm males were consistently larger than the controls throughout the study.

Significantly ($p \leq 0.05$) greater mean body weights were observed prior to and during the first mating and at the beginning of treatment prior to the second mating. Weight gains were similar between the 200 ppm males and controls during the first mating, however body weight gains during treatment for the second mating were only 50% of the control value. Because the 200 ppm males were larger than controls, food consumption was sporadically significantly greater than the control value.

TABLE 4. MALES: F_1 GENERATION MEAN BODY WEIGHTS AND FOOD CONSUMPTION (FIRST MATING)

Day of Study	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Body Weight (g)				
Day 1	153.1 ± 47.2	148.4 ± 34.5	153.0 ± 30.4	155.5 ± 36.9
Day 15	260.4 ± 67.0	289.0 ± 46.6	268.2 ± 47.1	273.3 ± 56.2
Day 29	342.4 ± 65.8	384.0 ± 40.7*	352.7 ± 43.8	360.8 ± 41.7
Day 50	428.8 ± 48.5	463.4 ± 43.9*	429.7 ± 50.6	428.4 ± 54.8
Day 71	492.1 ± 41.1	526.8 ± 40.9*	484.1 ± 51.3	474.9 ± 60.8
Day 92 (end of premating period)	516.7 ± 43.3	549.6 ± 46.4	510.4 ± 58.1	499.5 ± 51.2
Day 113 (end of mating period)	540.8 ± 47.2	565.3 ± 54.2	528.0 61.0	524.3 ± 49.9
Body Weight Gain, Day 1-113	387.1 ± 54.2	417.0 ± 58.6	375.6 ± 58.1	366.0 ± 47.2
Food Consumption Prior to First Mating (g)				
Day 1-8	24.8 ± 6.4	27.2 ± 4.8	24.8 ± 4.2	26.0 ± 4.7
Day 8-15	26.6 ± 6.8	29.8 ± 5.3	27.4 ± 5.8	28.4 ± 5.3
Day 22-29	29.5 ± 4.9	33.2 ± 2.8**	30.4 ± 3.6	30.5 ± 3.0
Day 43-50	30.4 ± 3.3	31.6 ± 3.6	29.7 ± 3.8	29.6 ± 4.3
Day 64-71	30.8 ± 2.5	32.5 ± 2.3	31.1 ± 3.1	28.9 ± 4.0
Day 92-96	28.5 ± 3.9	29.7 ± 2.5	27.9 ± 4.7	27.8 ± 3.1
Day 1-96	29.0 ± 2.9	31.4 ± 1.8*	29.2 ± 3.0	29.0 ± 2.9

Data taken from Table 31, p. 179-180, Table 32, p. 185-186, and Table 37, p. 195-196, MRID No. 428991-01.
*Significantly different from control, $p \leq 0.05$.
**Significantly different from control, $p \leq 0.01$.

TABLE 5. MALES: F_1 GENERATION MEAN BODY WEIGHTS AND FOOD CONSUMPTION (SECOND MATING)

Day of Study	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Body Weight (g)				
Day 1	577.9 ± 46.6	621.6 ± 53.8*	581.2 ± 72.3	576.9 ± 48.6
Day 8	605.3 ± 50.2	642.5 ± 60.9	593.9 ± 76.3	589.2 ± 48.7
Day 22	620.9 ± 58.4	653.4 ± 60.6	605.0 ± 76.3	599.9 ± 50.4
Day 36	625.5 ± 60.5	660.7 ± 62.2	616.7 ± 74.0	606.6 ± 50.4
Day 43 (end of premating period)	629.5 ± 57.7	656.7 ± 61.2	610.1 ± 79.5	605.1 ± 51.5
Day 64 (end of mating period)	619.8 ± 54.2	642.4 ± 63.4	596.6 ± 74.2	588.4 ± 48.0
Body Weight Gain, Day 1-64	41.9 ± 34.3	20.8 ± 18.5	15.4 ± 18.5**	11.5 ± 21.2**
Food Consumption Prior to Second Mating (g)				
Day 1-8	30.2 ± 3.4	31.4 ± 2.9	28.7 ± 4.1	29.2 ± 3.8
Day 8-15	30.3 ± 3.7	30.9 ± 2.8	29.4 ± 2.8	29.7 ± 3.5
Day 15-22	31.3 ± 4.1	32.0 ± 2.4	29.7 ± 2.9	28.9 ± 3.5*
Day 29-36	29.8 ± 3.2	32.3 ± 2.6*	30.4 ± 2.9	31.2 ± 4.0
Day 36-43	30.7 ± 2.7	32.3 ± 2.6	29.8 ± 4.2	31.3 ±
Day 1-43	30.2 ± 3.1	31.7 ± 2.3	29.4 ± 3.1	30.0 ± 3.3

Data taken from Table 54, p. 232, Table 55, p. 236, and Table 60, p. 244, MRID No. 428991-01.
*Significantly different from control, $p \leq 0.05$.
**Significantly different from control, $p \leq 0.01$.

Selected body weights and food consumption values for the F_1 females prior to the first and second matings are listed in Tables 6 and 7, respectively. No significant differences were observed in body weights or weight gains in treated F_1 females prior to the first or second mating as compared to controls. A slight dose-related reduction in body weight gains occurred prior to the first mating but this was not apparent prior to the second mating. Prior to the first mating, overall food consumption was significantly ($p \leq 0.05$) lower in the 2000 ppm females as compared to controls. All other food consumption values were comparable between treated and control groups.

TABLE 6. FEMALES: F_1 GENERATION MEAN BODY WEIGHTS AND FOOD CONSUMPTION PRIOR TO FIRST MATING				
Day of Study	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Body Weight (g)				
Day 1	137.4 ± 41.8	142.8 ± 28.2	145.1 ± 26.1	137.4 ± 27.8
Day 15	199.0 ± 35.1	206.4 ± 21.0	204.4 ± 21.0	194.9 ± 25.0
Day 29	237.8 ± 31.3	243.1 ± 19.0	239.6 ± 18.9	229.5 ± 23.8
Day 50	273.1 ± 27.6	278.1 ± 19.0	273.6 ± 18.7	261.1 ± 24.2
Day 71	286.5 ± 26.9	295.3 ± 23.4	290.4 ± 18.2	278.0 ± 24.8
Day 92	300.1 ± 29.0	304.0 ± 22.3	301.2 ± 20.2	288.6 ± 27.1
Body Weight Gain, Day 1-92	162.7 ± 36.3	161.2 ± 28.9	156.0 ± 30.6	150.6 ± 25.7
Food Consumption (g)				
Day 1-8	21.1 ± 4.4	21.8 ± 4.2	21.0 ± 2.0	19.4 ± 2.6
Day 8-15	21.4 ± 4.0	22.0 ± 4.8	20.7 ± 2.0	19.6 ± 2.4
Day 22-29	23.0 ± 3.5	22.7 ± 3.2	22.3 ± 3.4	21.2 ± 3.8
Day 43-50	21.8 ± 3.3	22.2 ± 4.4	21.4 ± 1.9	20.4 ± 3.0
Day 64-71	21.2 ± 3.3	22.0 ± 3.4	21.4 ± 3.6	21.1 ± 3.2
Day 92-96	22.0 ± 3.3	22.9 ± 4.7	22.3 ± 3.7	20.1 ± 2.5
Day 1-96	21.9 ± 2.9	22.2 ± 3.5	21.0 ± 1.5	19.9 ± 2.0*

Data taken from Table 31, p. 181-182, Table 32, p. 187-188, and Table 37, p. 197-198, MRID No. 428991-01.
*Significantly different from control, $p \leq 0.05$.

TABLE 7. FEMALES: F_1 GENERATION MEAN BODY WEIGHTS AND FOOD CONSUMPTION PRIOR TO SECONDMATING				
Day of Study	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Body Weight (g)				
Day 1	342.3 ± 31.2	343.2 ± 27.4	342.9 ± 30.4	327.3 ± 30.6
Day 8	338.1 ± 30.0	341.7 ± 23.5	339.7 ± 28.4	324.8 ± 31.5
Day 22	337.5 ± 32.2	341.2 ± 22.6	340.0 ± 31.7	327.1 ± 31.6
Day 36	342.4 ± 32.7	346.9 ± 24.7	345.1 ± 29.7	330.8 ± 34.7
Day 43	336.6 ± 35.9	343.4 ± 24.2	339.7 ± 30.8	326.8 ± 34.2
Body Weight Gain, Day 1-43	-6.1 ± 12.0[a]	0.1 ± 8.4	-3.2 ± 11.2	-0.5 ± 9.4

TABLE 7. FEMALES: F_1 GENERATION MEAN BODY WEIGHTS AND FOOD CONSUMPTION PRIOR TO SECONDMATING

Day of Study	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Food Consumption (g)				
Day 1-8	22.4 ± 2.7	22.4 ± 2.9	21.4 ± 2.4	20.7 ± 3.7
Day 15-22	22.9 ± 3.0	22.5 ± 2.2	21.7 ± 2.9	22.1 ± 3.8
Day 29-36	22.4 ± 2.3	23.1 ± 3.0	22.9 ± 3.0	21.9 ± 3.8
Day 36-43	*22.5 ± 3.4*	*22.6* ± 2.2	22.0 ± 2.9	21.5 ± 3.0
Day 1-43	22.2 ± 2.3	22.5 ± 2.3	22.0 ± 2.4	21.3 ± 3.0

Data taken from Table 54, p. 233, Table 55, p. 237, and Table 60, p. 245, MRID No. 428991-01.
[a]Excludes data for two animals for which body weights were incorrectly determined on day 43.

b. Gestation and lactation - Selected mean body weights, body weight gains, and food consumption values for P and F_1 females during gestation and lactation are summarized in Table 8. For P generation females, no compound or treatment-related effects were observed on body weights, body weight gains, or food consumption. For the F_1 females during gestation and lactation of litter A, significantly reduced body weight gains (88%) of the 2000 ppm group during gestation resulted in significantly reduced mean body weight (93%) on GD 20 as compared to controls ($p \leq 0.05$). For litter B, the GD 20 mean body weight of the 630 ppm group F_1 females was significantly ($p \leq 0.05$) less than the control group value (93%); mean body weight in the high-dose group was also reduced (94% of control) but did not reach statistical significance. Food consumption was significantly reduced in the 2000 ppm animals ($p \leq 0.05$) during gestation and in 630 ppm animals ($p \leq 0.01$) during lactation of litter B.

TABLE 8. SELECTED MEAN BODY WEIGHTS, BODY WEIGHT GAIN, AND FOOD CONSUMPTION VALUES FOR PREGNANT AND NURSING RATS FED TOPSIN-M FOR TWO GENERATIONS

Observation/Gestation day	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
P Generation				
Mean body weight (g)				
Day 0 of gestation	295.1 ± 21.3	288.2 ± 18.9	292.4 ± 25.0	290.3 ± 19.9
Day 20 of gestation	428.4 ± 36.8	420.9 ± 28.3	427.0 ± 36.1	423.0 ± 26.7
Day 1 of lactation	322.4 ± 26.8	325.4 ± 20.6	330.1 ± 32.3	325.0 ± 21.0
Day 21 of lactation	347.5 ± 26.6	345.4 ± 18.9	355.1 ± 23.3	352.4 ± 25.3

TABLE 8. SELECTED MEAN BODY WEIGHTS, BODY WEIGHT GAIN, AND FOOD CONSUMPTION VALUES FOR PREGNANT AND NURSING RATS FED TOPSIN-M FOR TWO GENERATIONS

Observation/Gestation day	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Mean body weight gain (g)				
Day 0-20 of gestation	133.32 ± 27.99	132.77 ± 16.98	134.60 ± 21.86	132.73 ± 19.40
Day 1-21 of lactation	25.13 ± 21.21	20.00 ± 17.09	24.98 ± 27.04	27.38 ± 14.84
Mean food consumption (g/rat/day)				
Day 0-20 of gestation	25.8 ± 3.0	25.2 ± 2.0	25.0 ± 1.5	24.5 ± 1.9
Day 1-21 of lactation	56.1 ± 7.6	58.3 ± 7.1	55.2 ± 7.0	54.1 ± 5.0
F_1 Generation – Litter A				
Mean body weight (g)				
Day 0 of gestation	296.6 ± 24.6	307.8 ± 24.4	306.8 ± 26.0	282.2 ± 28.8
Day 20 of gestation	447.2 ± 31.9	455.1 ± 34.3	456.9 ± 35.9	414.9 ± 40.6*
Day 1 of lactation	344.6 ± 25.6	349.1 ± 24.4	346.0 ± 23.3	310.5 ± 34.0
Day 21 of lactation	357.0 ± 21.0	364.0 ± 28.2	375.1 ± 31.6	332.1 ± 22.6
Mean body weight gain (g)				
Day 0-20 of gestation	150.58 ± 15.98	147.34 ± 22.31	150.14 ± 19.11	132.65 ± 25.00*
Day 1-21 of lactation	12.33 ± 15.18	14.94 ± 11.59	29.07 ± 24.58	21.60 ± 21.96
Mean food consumption (g/rat/day)				
Day 0-20 of gestation	27.5 ± 2.7	27.2 ± 3.1	27.4 ± 2.9	24.4 ± 2.0
Day 1-21 of lactation	43.8 ± 7.5	45.7 ± 10.6	45.6 ± 9.9	35.9 ± 5.6

TABLE 8. CONTINUED

Observation/Gestation day	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
F_1 Generation – Litter B				
Mean body weight (g)				
Day 0 of gestation	337.5 ± 30.0	340.1 ± 27.2	325.9 ± 28.2	321.6 ± 27.8
Day 20 of gestation	470.7 ± 39.6	465.9 ± 34.5	436.1 ± 43.6*	441.7 ± 31.0
Day 1 of lactation	368.6 ± 24.5	363.7 ± 37.1	355.6 ± 35.0	348.8 ± 29.3
Day 21 of lactation	385.6 ± 25.4	372.3 ± 29.2	372.0 ± 36.3	368.2 ± 30.3
Mean body weight gain (g)				
Day 0-20 of gestation	133.12 ± 21.41	116.82 ± 25.71	110.14 ± 31.23	120.07 ± 18.26
Day 1-21 of lactation	15.08 ± 27.93	8.61 ± 28.9	16.34 ± 14.91	19.43 ± 22.52

TABLE 8. CONTINUED				
Observation/Gestation day	Treatment Group			
	0 ppm	200 ppm	630 ppm	2000 ppm
Mean food consumption (g/rat/day)				
Day 0-20 of gestation	27.9 ± 2.2	26.8 ± 2.3	25.9 ± 3.1	25.3 ± 2.3*
Day 1-21 of lactation	65.2 ± 7.8	58.7 ± 8.3	52.7 ± 12.1**	57.4 ± 6.5

Data taken from Tables 5-8, pages 125, 127, 128, and 130; Tables 10 and 11, pages 137 and 139; Tables 33-36, pages 189, 191, 192, and 194; Tables 38 and 39, pages 201 and 203; Tables 56-59, pages 238, 240, 241, and 243; Table 61 and 62, pages 248 and 250, MRID No. 428991-01.
*Significantly different from control, $p \leq 0.05$.
**Significantly different from control, $p \leq 0.01$.

3. Test Substance Intake

Based on weekly food consumption and body weight data, the doses expressed as mg of test substance/kg body weight/day during the premating period for males and females and during gestation and lactation for females are presented in Table 9. The time weighted averages of total compound intake calculated from the table are 0, 13.7, 43.3 or 138.9 mg/kg/day for males and 0, 15.5, 54.0 or 172.0 mg/kg/day for females.

TABLE 9. TEST SUBSTANCE INTAKE IN RATS FED TOPSIN-M FOR TWO GENERATIONS (mg/kg/day)[a]			
Study Interval	Concentration in Diet		
	200 ppm	630 ppm	2000 ppm
P Generation			
Males - Premating	13.9 ± 2.8	44.3 ± 8.3	141.7 ± 24.4
Females - Premating	16.3 ± 1.7	51.5 ± 5.7	161.0 ± 14.8
Females - Gestation	14.2 ± 0.3	44.0 ± 1.5	136.8 ± 1.9
Females - Lactation	30.6 ± 10.1	89.7 ± 31.4	284.6 ± 94.7
F_1 Generation - First Mating			
Males - Premating	15.3 ± 4.1	47.7 ± 11.3	152.5 ± 40.0
Females - Premating	17.4 ± 3.1	52.8 ± 8.9	167.5 ± 26.2
Females - Gestation	14.3 ± 0.8	45.1 ± 2.4	139.6 ± 3.0
Females - Lactation	23.8 ± 3.5	72.6 ± 14.6	209.8 ± 21.5
F_1 Generation - Second Mating			
Males - Premating	9.7 ± 0.2	30.7 ± 0.5	100.7 ± 2.4
Females - Premating	13.1 ± 0.2	40.6 ± 0.8	130.3 ± 3.1
Females - Gestation	13.4 ± 0.5	42.3 ± 0.5	132.9 ± 2.3
Females - Lactation	28.6 ± 9.4	82.1 ± 25.3	288.6 ± 81.2

Data derived from Tables 12-14, pages 141-146; Tables 40-42, pages 205-210; and Tables 63-65, pages 252-255, MRID No. 428991-01.
[a]Overall group means calculated by reviewer from weekly group means; weekly means were based on weekly body weight measurements and nominal diet concentrations.

4. Hormone analysis

No treatment- or dose-related effects on the serum levels of T_3, T_4, or TSH were observed in the parental animals of either generation. T_3 and T_4 levels were occasionally significantly ($p \leq 0.05$) decreased at various sampling times for all treated groups of males and females of the P generation as compared to controls. High-dose males and females of both generations tended toward higher TSH levels at week 8 and at necropsy; however, these levels were <2.5 times the control level so are not considered biologically significant.

TABLE 10. T_3, T_4 AND TSH LEVELS IN MALES AT VARIOUS TIME INTERVALS (10 ANIMALS EACH IN P GENERATION)

Time	Controls	200 ppm	630 ppm	2000 ppm
T_3 (ng/ml)				
Week 1	0.64 ± 0.13	0.62 ± 0.08	0.59 ± 0.10	0.51 ± 0.09
Week 8	0.50 ± 0.11	0.56 ± 0.09	0.61 ± 0.13	0.57 ± 0.12
Necropsy	0.70 ± 0.12	0.79 ± 0.14	0.90 ± 0.13*	0.74 ± 0.07
T_4 (µg/100 ml)				
Week 1	4.8 ± 0.7	4.1 ± 0.6*	4.3 ± 0.4	3.5 ± 0.5*
Week 8	5.2 ± 0.7	5.0 ± 0.7	5.6 ± 0.7	4.5 ± 0.7*
Necropsy	4.2 ± 1.2	3.9 ± 1.0	4.7 ± 1.3	4.3 ± 1.1
TSH (ng/ml)				
Week 1	2.9 ± 1.6	3.7 ± 1.1	3.4 ± 1.6	3.9 ± 2.1
Week 8	4.2 ± 2.2	5.7 ± 2.2	4.6 ± 2.3	7.8 ± 4.0*
Necropsy	2.8 ± 1.3	3.1 ± 1.7	3.3 ± 2.7	5.0 ± 2.6

* Significantly different from control (95% confidence interval). Data summarized from tables 16 through 18.

TABLE 10 CONTINUED. T_3, T_4 AND TSH LEVELS IN FEMALES AT VARIOUS TIME INTERVALS (10 ANIMALS EACH IN P GENERATION)

Time	Controls	200 ppm	630 ppm	2000 ppm
T_3 (ng/ml)				
Week 1	0.82 ± 0.07	0.81 ± 0.05	0.71 ± 0.09*	0.76 ± 0.11
Week 8	0.70 ± 0.10	0.65 ± 0.11	0.63 ± 0.10	0.63 ± 0.12
Necropsy	0.84 ± 0.10	0.77 ± 0.07	0.76 ± 0.12	0.71 ± 0.09*
T_4 (µg/100 ml)				
Week 1	4.5 ± 0.6	4.2 ± 0.6	3.7 ± 0.7*	3.2 ± 0.3*
Week 8	3.9 ± 0.7	3.4 ± 0.6	3.6 ± 0.7	3.3 ± 0.4
Necropsy	2.7 ± 0.7	2.7 ± 0.4	3.1 ± 0.6	2.8 ± 0.6
TSH (ng/ml)				
Week 1	1.7 ± 0.5	1.8 ± 0.4	1.6 ± 1.1	1.8 ± 0.8
Week 8	1.4 ± 0.4	1.8 ± 0.5	2.0 ± 0.6*	3.2 ± 1.6*
Necropsy	3.0 ± 1.1	2.3 ± 0.7	3.0 ± 0.9	3.5 ± 1.6

* Significantly different from control (95% confidence interval). Data summarized from tables 16 through 18.

TABLE 11. T_3, T_4 AND TSH LEVELS IN MALES AT VARIOUS TIME INTERVALS (10 AMINALS EACH IN F_1 GENERATION)				
Time	Controls	200 ppm	630 ppm	2000 ppm
T_3 (ng/ml)				
Week 8	0.72 ± 0.19	0.65 ± 0.08	0.59 ± 0.07	0.59 ± 0.07
Necropsy	0.76 ± 0.14	0.77 ± 0.17	0.73 ± 0.07	0.70 ± 0.14
T_4 (µg/100 ml)				
Week 8	4.8 ± 0.6	4.9 ± 0.4	4.6 ± 0.4	4.8 ± 0.7
Necropsy	3.5 ± 0.7	3.5 ± 0.9	3.5 ± 0.6	3.5 ± 0.7
TSH (ng/ml)				
Week 8	3.4 ± 1.3	4.1 ± 1.7	5.3 ± 2.2	6.9 ± 3.9*
Necropsy	4.6 ± 2.4	3.6 ± 1.4	3.8 ± 1.5	4.2 ± 2.7

* Significantly different from control (95% confidence interval). Data summarized from tables 67 through 69.

TABLE 11 CONTINUED. T_3, T_4 AND TSH LEVELS IN FEMALES AT VARIOUS TIME INTERVALS (10 ANIMALS EACH IN F_1 GENERATION)				
Time	Controls	200 ppm	630 ppm	2000 ppm
T_3 (ng/ml)				
Week 8	0.78 ± 0.11	0.79 ± 0.08	0.77 ± 0.11	0.80 ± 0.22
Necropsy	0.79 ± 0.12	0.81 ± 0.08	0.71 ± 0.08	0.77 ± 0.18
T_4 (µg/100 ml)				
Week 8	3.7 ± 0.8	3.7 ± 0.8	3.5 ± 0.6	3.3 ± 0.7
Necropsy	2.5 ± 0.6	2.7 ± 0.4	2.7 ± 0.4	2.9 ± 0.6
TSH (ng/ml)				
Week 8	1.5 ± 1.0	3.0 ± 1.0	2.8 ± 0.9	4.3 ± 2.3
Necropsy	3.4 ± 2.0	3.0 ± 1.0	2.8 ± 0.9	4.3 ± 2.3

* Significantly different from control (95% confidence interval). Data summarized from tables 67 through 69.

5. Necropsy results

a. Organ weights – Organ weights at necropsy for both the P and F_1 generations are given in Tables 12 and 13. High-dose P generation males and females had significantly ($p \leq 0.05$) increased absolute liver and thyroid weights. In the F_1 animals, males had significantly increased absolute liver (200 and 2000 ppm) and thyroid weights (2000 ppm) while females in all dose groups had increased absolute thyroid weights as

compared to controls. Relative organ weights were calculated from the provided absolute organ weight tables. Although no statistical analyses were conducted on these data, it appears that they parallel the absolute organ weight data.

TABLE 12. ABSOLUTE ORGAN WEIGHTS FROM RATS FED TOPSIN-M

	Males				Females			
Organ	0 ppm	200 ppm	630 ppm	2000 ppm	0 ppm	200 ppm	630 ppm	2000 ppm
P Generation								
Liver (g)	24.4 ± 5.4	25.0 ± 4.9	24.7 ± 5.3	28.8 ± 5.5*	12.1 ± 1.8	12.1 ± 1.2	12.1 ± 1.8	13.6 ± 1.5*
Thyroid (mg)	29 ± 7	31 ± 6	29 ± 6	39 ± 10*	23 ± 5	22 ± 5	23 ± 4	30 ± 6*
F_1 Generation								
Liver (g)	20.6 ± 4.1	25.3 ± 4.3*	23.0 ± 4.2	26.0 ± 4.5*	13.3 ± 2.2	13.7 ± 1.7	13.4 ± 1.3	14.3 ± 2.5
Thyroid (mg)	28 ± 6	31 ± 9	30 ± 5	36 ± 6*	23 ± 3	26 ± 5*	26 ± 3*	29 ± 6*

Data taken from Tables 19 and 70, pages 154-155 and 263-264, respectively, MRID No. 428991-01.
*Significantly different from control, $p < 0.05$.

TABLE 13. RELATIVE ORGAN WEIGHTS FROM RATS FED TOPSIN-M

	Males				Females			
Organ	0 ppm	200 ppm	630 ppm	2000 ppm	0 ppm	200 ppm	630 ppm	2000 ppm
P Generation								
Liver (g)	0.038	0.040	0.040	0.046	0.037	0.038	0.037	0.042
Thyroid (mg)	0.045	0.049	0.047	0.063	0.070	0.070	0.070	0.093
F_1 Generation								
Liver (g)	0.032	0.038	0.037	0.043	0.037	0.037	0.038	0.043
Thyroid (mg)	0.044	0.046	0.049	0.060	0.064	0.071	0.073	0.086

Data calculated by HED reviewer from Tables 19 and 70, pages 154-155 and 263-264, respectively, MRID No. 428991-01. No statistical analyses were conducted on relative weights.

b. Pathology -

1) Macroscopic examination - No dose- or treatment-related alterations were observed by gross examination at necropsy in either the P or F_1 generation parental animals.

2) Microscopic examination - Incidence rates of treatment-related liver and thyroid lesions are listed in Tables 14 and 15. An increased incidence of hepatocyte hypertrophy was seen in high-dose males and females of both generations. Increased incidences of thyroid follicular cell hyperplasia and hypertrophy were seen in high-dose P generation males and females and in high-dose F_1 generation males. Generally, minimal to slight hepatocellular hypertrophy and thyroid follicular cell hypertrophy and hyperplasia were observed in both the low and mid-dose P generation males. These effects were observed in the F_1 generation but appeared in fewer animals and were less severe. In females, the effects were considerably less than in males.

TABLE 14. HISTOPATHOLOGICAL FINDINGS IN RATS FED TOPSIN-M (STATISTICAL ANALYSIS OF HIGH DOSE COMPARED TO CONTROL GROUPS

	Males		Females	
Organ	0 ppm	2000 ppm	0 ppm	2000 ppm
P Generation				
Hepatocyte hypertrophy	0/25[a]	22/25**	0/24	18/25**
Thyroid				
Follicular cell hypertrophy	0/25	22/25**	0/24	6/25*
Follicular cell hyperplasia	1/25	21/25**	0/24	5/25*
F_1 Generation				
Hepatocyte hypertrophy	0/25	6/24**	0/24	5/25*
Thyroid				
Follicular cell hypertrophy	0/25	6/24**	0/24	0/22
Follicular cell hyperplasia	0/25	20/24**	0/24	0/22

Data taken from Appendix 72, pages 1233-1283, MRID No. 428991-01.
[a]Number affected/number examined.
Incidence rate significantly different from control: *p ≤ 0.05; **p ≤ 0.01 (calculated by reviewer using Fisher's Exact test).

TABLE 15. INCIDENCES AND GRADINGS OF LIVER AND THYROID LESIONS

	Males				Females			
Dose (ppm)	0	200	630	2000	0	200	630	2000
P Generation								
Liver								
Hepatocellular hypertrophy	0	9	14	23	0	1	3	20
Minimal	0	7	10	13	0	1	3	18
Slight	0	2	3	7	0	0	0	2
Moderate	0	0	1	3	0	0	0	0
Thyroid								
Follicular cell hypertrophy	0	9	7	22	0	0	1	4
Minimal	0	8	3	9	0	0	0	3
Slight	0	0	4	13	0	0	1	1
Moderate	0	1	0	0	0	0	0	0
Follicular cell hyperplasia	0	6	13	17	0	0	2	6
Minimal	0	5	13	14	0	0	2	5
Slight	0	1	0	3	0	0	0	1
F_1 Generation								
Liver								
Hepatocellular hypertrophy	0	3	6	11	0	1	1	15
Minimal	0	3	4	8	0	0	1	10
Slight	0	0	1	3	0	1	0	2
Moderate	0	0	1	0	0	0	0	3
Thyroid								
Follicular cell hypertrophy	0	3	2	1	0	0	0	0
Minimal	0	2	2	0	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Moderate	0	1	0	0	0	0	0	0
Follicular cell hyperplasia	0	4	4	10	0	0	1	2
Minimal	0	3	4	9	0	0	1	2
Slight	0	1	0	1	0	0	0	0

B. REPRODUCTIVE TOXICITY

1. Reproductive performance

The reproductive performance of parental animals is summarized in Tables 16a and 16b. No treatment-related effects were noted in either generation. In both matings of the F_1 generation, the 630 ppm group produced fewer litters than any other group. However, a dose-related trend was not apparent.

TABLE 16a. REPRODUCTIVE PERFORMANCE IN P GENERATION RATS FED TOPSIN - M

Observation	Treatment Groups			
	0 ppm	200 ppm	630 ppm	2000 ppm
Mean cohabitation days (until GD 0)	2.0 ± 1.5	1.7 ± 0.9	1.8 ± 1.1	2.5 ± 2.6
Males				
Number mated	25	25	25	25
Number inseminating females	20	23	23	25
Females				
Number mated	25	25	25	25
Number pregnant	21	20	19	19
Number plug- or sperm-positive	24	25	25	25
Number with sperm not detected, littered	1	0	0	0
Number delivering	21	20	19	19
Indices (%)				
Insemination index	100	100	100	100
Fecundity index	84	80	76	76
Fertility index	84	80	76	76
Gestation index	100	100	100	100
Mean gestation interval (days)	22.0 ± 0.6	22.0 ± 0.2	21.8 ±0.5	21.9 ± 0.4

Data taken from Tables 1, 15, and 21, pages 111, 147, and 159, respectively, and from Appendix 14, pages 530-533, MRID No. 428991-01.

TABLE 16b. REPRODUCTIVE PERFORMANCE IN F_1 GENERATION RATS FED TOPSIN - M

Observation	Treatment Groups			
	0 ppm	200 ppm	630 ppm	2000 ppm
First Mating				
Mean cohabitation days (until GD 0)	2.8 ± 2.6	2.6 ± 2.4	3.6 ± 3.5	2.3 ± 1.3
Males				
Number mated	25	25	24	24
Number inseminating females	21	23	20	24
Females				
Number mated	25	25	25	25
Number pregnant	21	21	17	21
Number plug- or sperm-positive	24	25	24	25
Number with sperm not detected, littered	0	0	0	0
Number delivering (%)	21	21	17	21
Indices (%)				
Insemination index	96	100	96	100
Fecundity index[a]	88	84	71	84
Fertility index[a]	84	84	68	84
Gestation index	100	100	100	100
Mean gestation interval (days)	21.9 ± 0.4	22.0 ± 0.2	21.8 ± 0.4	22.1 ± 0.4
Second Mating				
Mean cohabitation days (until GD 0)	2.0 ± 1.4	2.2 ± 1.2	2.5 ± 2.2	2.4 ± 1.8
Males				
Number mated	25	24	24	24
Number inseminating females	21	22	17	20
Females				
Number mated	25	24	25	25
Number pregnant	17	19	14	15
Number plug- or sperm-positive	21	23	22	22
Number with sperm not detected, littered	1	0	0	0
Number delivering (%)	17	19	14	15

TABLE 16b. Continued				
Observation	Treatment Groups			
	0 ppm	200 ppm	630 ppm	2000 ppm
Indices (%)				
Insemination index	84	96	88	88
Fecundity index[a]	81	83	64	68
Fertility index[a]	68	79	56	60
Gestation index	100	100	100	100
Mean gestation interval (days)	22.1 ± 0.4	22.3 ± 0.6	22.4 ± 0.8	22.2 ± 0.4

Data taken from Tables 29, 43, and 45, pages 175, 211, and 214-218, and Tables 52, 66 and 72, pages 228, 256, and 267-271, respectively, and from Appendices 38, pages 857-860 and 61, pages 1118-1121, MRID No. 428991-01.
[a]Calculated by reviewer using number of animals delivering as number pregnant.

2. Viability and clinical signs

Viability and clinical observations of offspring from the P and F_1 generations are summarized in Tables 17a and 17b, respectively. Mean litter sizes, survival indices, and sex ratios were not different between treated and control groups for litters from the P generation (F_1 offspring). Following the first mating of the F_1 animals, a high rate of death occurred in F_{2a} pups from all treated groups and the control group during lactation. This was apparent by the decreases in number of live pups/litter between lactation day 1 and 21 and the low weaning indices calculated for all groups. This rate of death was not repeated with the offspring of the second mating of the F_1 animals. For F_{2b} pups, mean litter sizes, sex ratios, and survival indices were comparable between treated and control groups. However, fewer litters were produced in all groups, including the control, from the second mating than from the first mating.

TABLE 17a. VIABILITY AND CLINICAL OBSERVATIONS OF P GENERATION OFFSPRING DURING LACTATION				
Observation/study time	0 ppm	200 ppm	630 ppm	2000 ppm
Number of litters	21	20	19	19
Total number of pups	304	280	257	261
Number pups born alive	302	280	253	259
Number pups stillborn	2	0	4	2
Mean litter size at delivery	14.48 ± 3.08	14.00 ± 2.13	13.53 ± 3.94	13.74 ± 3.09
Mean number live pups/litter				
Day 1	14.40 ± 2.93	13.85 ± 2.01	13.33 ± 4.07	13.32 ± 3.07
Day 4 (precull)	13.60 ± 2.68	12.90 ± 2.86	12.44 ± 3.88	12.74 ± 2.96
Day 4 (postcull)	7.95 ± 0.22	7.85 ± 0.49	7.61 ± 1.24	7.89 ± 0.46
Day 21	7.05 ± 1.61	7.58 ± 0.96	7.17 ± 1.65	7.33 ± 1.03
Number litters weaned	20	19	18	18
Survival Indices (%)				
Live birth index	99	100	99	99
Viability index	89	93	89	94

TABLE 17a. VIABILITY AND CLINICAL OBSERVATIONS OF P GENERATION OFFSPRING DURING LACTATION				
Observation/study time	0 ppm	200 ppm	630 ppm	2000 ppm
Weaning index	89	90	94	88
Sex ratio (% male) - day 0	47	47	45	50
Sex ratio (% male) - day 4 (precull)	48	49	45	49

Data taken from Table 21, pages 159-163, MRID No. 428991-01.

TABLE 17b. VIABILITY AND CLINICAL OBSERVATIONS OF F_1 GENERATION OFFSPRING DURING LACTATION				
Observation/study time	0 ppm	200 ppm	630 ppm	2000 ppm
F_{2a} Litter				
Number of litters	21	21	17	21
Total number of pups	311	315	273	279
Number pups born alive	307	305	269	263
Number pups stillborn	4	10	4	12
Mean litter size at delivery	14.81 ± 2.02	15.00 ± 2.92	16.06 ± 2.38	13.29 ± 4.04
Mean number live pups/litter				
Day 1	14.62 ± 1.83	13.71 ± 3.05	15.29 ± 2.34	11.95 ± 4.14
Day 4 (precull)	13.38 ± 2.64	11.80 ± 4.11	13.41 ± 3.66	10.47 ± 4.86
Day 4 (postcull)	7.90 ± 0.44	7.45 ± 1.47	7.88 ± 0.49	6.89 ± 1.66*
Day 21	2.86 ± 1.77	3.60 ± 1.96	3.00 ± 1.67	2.00 ± 0.87
Number litters weaned	7	10	6	9
Survival Indices (%)				
Live birth index	99	97	99	95
Viability index	92	78	84	74
Weaning index	12	24	13	13
Sex ratio (% male) - day 0	46	47	49	51
Sex ratio (% male) - day 4 (precull)	47	53	49	55
F_{2b} Litter				
Number of litters	17	19	14	15
Total number of pups	213	190	132	181
Number pups born alive	210	185	130	181
Number pups stillborn	3	4	2	0
Mean litter size at delivery	12.53 ± 4.02	10.00 ± 4.57	9.43 ± 4.29	12.07 ± 3.31
Mean number live pups/litter				
Day 1	12.29 ± 3.74	10.11 ± 4.47	8.43 ± 5.00	12.07 ± 3.31
Day 4 (precull)	11.88 ± 3.69	9.69 ± 4.47	8.33 ± 5.03	11.79 ± 3.24
Day 4 (postcull)	7.56 ± 1.50	7.00 ± 2.03	5.92 ± 2.81	7.64 ± 1.08
Day 21	7.13 ± 1.89	6.85 ± 1.57	6.30 ± 2.63	7.15 ± 1.68
Number litters weaned	16	13	10	13

TABLE 17b. VIABILITY AND CLINICAL OBSERVATIONS OF F_1 GENERATION OFFSPRING DURING LACTATION				
Observation/study time	0 ppm	200 ppm	630 ppm	2000 ppm
Survival Indices (%)				
Live birth index	99	94	98	100
Viability index	91	77	69	90
Weaning index	94	74	79	87
Sex ratio (% male) - day 0	56	49	53	53
Sex ratio (% male) - day 4 (precull)	55	51	44	52

Data taken from Tables 45 and 72, pages 214-218 and 267-271, respectively, MRID No. 428991-01.
*Significantly different from control, $p \leq 0.05$.

3. Body weight

Selected means for pup body weight/litter are summarized in Table 18. No statistically significant differences occurred in mean pup weights from any treated group at any time during lactation of the F_1 or F_{2a} pups. However, F_{2b} pups gained less weight than controls with day 21 body weights of 2000 ppm group males and females being 88% of the control value. When mean pup weights for the F_{2b} litters were analyzed by covariance analysis (ANCOVA) to account for the number of pups per litter, significantly lower weights as compared to control were seen for 630 ppm males and females on day 1, 2000 ppm males on day 21, and 630 and 2000 ppm females on day 21.

TABLE 18. GROUP MEAN BODY WEIGHT OF OFFSPRING DURING LACTATION (grams)				
Day of Lactation	0 ppm	200 ppm	630 ppm	2000 ppm
P Generation - F_1 Offspring				
Males				
Day 1	6.78 ± 0.64	6.79 ± 0.57	6.50 ± 0.67	6.68 ± 0.57
Day 4 (postcull)	9.07 ± 1.32	9.05 ± 1.57	8.65 ± 1.71	9.02 ± 1.21
Day 21	48.94 ± 6.57	48.31 ± 5.3	45.75 ± 6.59	44.61 ± 5.76
Females				
Day 1	6.43 ± 0.71	6.41 ± 0.59	6.36 ± 0.79	6.41 ± 0.61
Day 4 (postcull)	8.50 ± 1.64	8.84 ± 1.09	8.77 ± 1.94	8.66 ± 1.02
Day 21	47.35 ± 6.01	46.67 ± 6.30	46.11 ± 6.02	42.67 ± 4.94
F_1 Generation – F_{2a} Offspring				
Males				
Day 1	6.79 ± 0.64	6.47 ± 0.56	6.23 ± 0.62	6.70 ± 0.68
Day 4 (postcull)	7.71 ± 1.65	7.32 ± 1.69	6.98 ± 1.61	7.20 ± 1.43
Day 21	49.52 ± 13.52	47.88 ± 7.05	51.64 ± 10.44	43.82 ± 11.67
Females				
Day 1	6.25 ± 0.48	6.14 ± 0.60	5.77 ± 0.62	6.29 ± 0.75
Day 4 (postcull)	7.26 ± 1.31	7.32 ± 1.76	6.56 ± 1.76	7.05 ± 1.66
Day 21	46.55 ± 13.00	40.78 ± 12.59	44.15 ± 12.50	44.87 ± 8.25
F_1 Generation – F_{2b} Offspring				
Males				
Day 1	7.23 ± 0.56	7.17 ± 0.57	6.73 ± 0.71[a,**]	7.03 ± 0.50
Day 4 (postcull)	10.39 ± 1.30	9.59 ± 2.29	9.41 ± 1.63	9.30 ± 1.13
Day 21	54.70 ± 5.68	52.34 ± 5.50	49.73 ± 8.26	47.90 ± 4.54[a,*]
Females				
Day 1	6.79 ± 0.50	6.64 ± 0.50	6.30 ± 0.60[a,**]	6.49 ± 0.50
Day 4 (postcull)	9.66 ± 0.89	9.17 ± 1.97	8.09 ± 1.99	8.68 ± 1.21
Day 21	51.64 ± 5.11	51.25 ± 5.99	45.36 ± 8.59[a,*]	45.28 ± 4.53[a,*]

Data taken from Tables 21, 45, and 72, pages 159-163, 214-218, and 267-271, respectively MRID No. 428991-01.
[a]Covariate adjusted mean significantly different from control: *p < 0.05, **p < 0.01 (Covariance analysis).

4. Physical and functional development

a. Physical development – There were no significant treatment-related differences between treated and control groups of either generation for the physical development parameters of pinna unfolding, incisor eruption, and eye opening.

b. Functional tests – There were no significant treatment-related differences between treated and control groups of either generation in the percentage of pups with positive response for surface righting reflex, gripping reflex, pupillary reflex, or auditory reflex.

5. Necropsy results

No dose- or treatment-related abnormalities were observed at necropsy in pups from either generation.

III. DISCUSSION

Male and female Sprague-Dawley rats were fed up to 2000 ppm Topsin-M in the diet for two generations. One litter was produced in the first generation and two were produced in the second generation.

A. SYSTEMIC TOXICITY

No treatment-related effects were seen on mortality, clinical signs, feed consumption, or gross pathology of P or F_1 generation parental animals of either sex. The deaths of four F_1 females were probably from excessive internal hemorrhaging after delivery instead of a direct compound-related effect. After approximately day 50 of treatment, a dose-related trend toward decreased body weights in males of both generations was observed. Significantly increased liver and thyroid weights occurred in P generation males and females, increased liver weights occurred in F_1 males, and increased thyroid weights occurred in F_1 males and females. Liver hypertrophy may have included induction of liver enzymes. Liver enzyme induction could account for the slightly decreased levels of T_3 and T_4 which, in turn, could have caused the slightly greater TSH levels as a compensatory mechanism. Constant stimulation of the thyroid by elevated TSH would explain the hyperplasia/hypertrophy in the thyroid.

The systemic LOEL for this study is < 200 ppm based on hepatocellular hypertrophy and thyroid follicular cell hypertrophy/hyperplasia at all dose levels and decreased body weight gains in males and increased liver and thyroid weights in both sexes at the highest dose level. This LOEL is considered to be a borderline NOEL/LOEL because the effects on the thyroid and liver at 200 ppm were minimal and they were less in the succeeding generation.

B. REPRODUCTIVE TOXICITY

Mean litter sizes, survival indices, and sex ratios were not different between treated and control groups for the F_1 or F_{2b} litters. Excessive deaths of the F_{1a} pups is unexplained but is probably not compound-related as controls were affected as well as treated groups. No statistically significant differences occurred in mean pup weights from any treated group at any time during lactation of the F_1 or F_{2a} pups. However F_{2b} pups gained less weight than controls with day 21 body weights of males and females only 88% of the control value. Covariance analysis (ANCOVA) of mean pup weights for the F_{2b} litters, to account for the number of pups per litter, revealed significantly lower weights as compared to control for 630 ppm males and females on day 1, 2000 ppm males on day 21, and 630 and 2000 ppm females on day 21. Decreased pup weights cannot be explained by reduced dam weights during lactation since high-dose dams actually gained slightly more than controls. However, reduced pup weights did not impair maturation as no differences were seen in physical developmental parameters or functional test responses between treated and control pups of either generation.

The reproductive toxicity LOEL for this study is 630 ppm based on reduced body weights of the F_{2b} pups during lactation. The NOEL is 200 ppm. This LOEL is also borderline because the decrease in pup weights was minimal.

C. STUDY DEFICIENCIES

The authors did not specifically state whether the technical form of the chemical was used. Rats were only 6 weeks old at the beginning of the study as opposed to 8 weeks which is stated in the acceptance criteria.

These deficiencies are minimal and do not alter the analysis of the study.

D. CORE CLASSIFICATION

Acceptable.

13544

R134128

Chemical: Thiophanate-methyl

PC Code: 102001
HED File Code: 61400 SRRD DERs
Memo Date: 3/23/1999
File ID: 00000000
Accession #: 412-07-0027

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